

## **CASE REPORT**

# **Intrathecal tramadol may cause respiratory depression**

Waqas Alam<sup>\*1</sup>, Mobasher Ahmad Saeed, MCPS, FCPS<sup>2</sup>,  
Khan Muhammad Yaqub, FCPS (Anesth), FCPS (Critical Care)<sup>3</sup>

<sup>\*1</sup>Registrar; <sup>2</sup>Associate Professor; <sup>3</sup>Consultant Anesthesia and Critical Care Medicine  
Department of Anesthesia & Intensive Care, PNS Shifa Hospital, Karachi, (Pakistan)

**Correspondence:** Dr. Waqas Alam, Department of Anesthesia and Intensive Care  
PNS Shifa Hospital, Lily Bridge Rd, Karachi (Pakistan); Phone: 0092 342 5558886; E-mail: [waqacalam@gmail.com](mailto:waqacalam@gmail.com).

## **ABSTRACT**

Opioids such as morphine and fentanyl have been used in neuraxial anesthesia to prolong the analgesic effects since long, but these have frequently been associated with few adverse effects e.g. nausea, vomiting, pruritus and rarely respiratory depression. Tramadol has also been used in epidural as well as spinal anesthesia, and respiratory depression has not been reported with its intrathecal use. We present a case in which 20 mg of intrathecal tramadol produced signs of opioid overdose including respiratory depression. The side effects were reversed with naloxone confirming our suspicion that these were caused by tramadol. We recommend adequate monitoring and vigilance for tramadol as is used for other intrathecal opioids.

**Key words:** Tramadol; Respiratory depression; Intrathecal; Opioid overdose

**Citation:** Alam W, Saeed MA, Yaqub KM. Intrathecal tramadol may cause respiratory depression. *Anaesth Pain & Intensive Care* 2017;21(1):87-89

**Received:** 28 Dec 2016; **Reviewed:** 28 Dec 2016, 21 Jan 2017; **Corrected & Accepted:** 15 Mar 2017

## **INTRODUCTION**

Opioids have been used as an adjunct to neuraxial anesthesia to reduce the dose and adverse effects of local anesthetics and to increase the duration of analgesia<sup>1,2</sup>. However use of opioids is associated with some adverse effects such as pruritus, nausea, vomiting and respiratory depression. Most feared complications for anesthesiologists is respiratory depression. Respiratory depression is reported with fentanyl and morphine.<sup>2,3</sup> And even respiratory depression can represent after many hours of injection.<sup>4</sup> Tramadol is a weak opioid and is safely used as intravenous analgesia. It is believed that it is not associated with respiratory depression and has less adverse effects and dependence than other strong opioids.<sup>5</sup> It has also been used in neuraxial anesthesia with local anesthetics.<sup>6,7</sup> Incidence of nausea and vomiting is reported with its use but respiratory depression is never reported. Here we are going to report respiratory depression with intrathecal tramadol. To our knowledge, it has

never been reported in literature before.

## **CASE REPORT**

A 28 years old male ASA 1 patient presented for knee arthroscopy and anterior cruciate ligament repair. Standard monitoring was applied. No premedication was given. Spinal anesthesia was given with 3 ml of 0.5% hyperbaric bupivacaine in L4,5 vertebral space. 20 mg tramadol (inj. Tramal®) was added to intrathecal injection to prolong the analgesic effects. Patient was comfortable and his heart rate was 78/min, blood pressure 115/72 mmHg and saturation was 99% on room air. After one hour patient became little uneasy and moving his upper body. His heart rate was 85/min, blood pressure was 110/75 mmHg and saturation of 97%. It was thought that patient was getting tired due to length of surgery and 2 mg midazolam was given. Patient became comfortable. But after few minutes his saturation started dropping and became 80% while his heart rate and blood pressure were same

He was not breathing and was non responsive to loud voice and painful stimulus. Immediately bag mask ventilation was started which was very easy. His saturation improved but he was still not breathing by himself and was not responding to painful stimulus. His pupils were checked and those were pinpoint and not reacting to light. Drugs were reviewed and it was suspected that it could be tramadol induced because none of the other drugs used present like this. Naloxone 0.4 mg was diluted in 10 ml distilled water. We started giving naloxone in boluses of 2 ml. After 4 ml of naloxone breathing effort of patient returned and he started responding to shaking and loud voice. Boluses of naloxone continued and patient improved. After complete injection he was fully awake, his pupils became normal, his breathing was normal. His heart rate was 82/min, blood pressure 123/78 mmHg and his saturation was 100%. After surgery patient was shifted to ICU for overnight observation. He remained stable and did not require additional dose of naloxone. On the basis of signs of opioid overdose and complete reversal after naloxone, we consider it as tramadol induced respiratory depression.

## DISCUSSION

Tramadol consists of two enantiomers which have analgesic activity via two different mechanisms. Metabolite of tramadol O-desmethyl-tramadol (M1) also shows analgesic activity. (+) Tramadol and the metabolite (+) M1 are agonists of the  $\mu$  (mu) opioid receptor. M1 has high affinity for  $\mu$  receptors as compared to parent drug. The two enantiomers of tramadol also inhibit serotonin and norepinephrine reuptake.<sup>5</sup> A study was conducted in cats in which  $\mu$  receptors are implicated for respiratory depression in tramadol overdose.<sup>8</sup>

Tramadol is widely used as oral and intravenous analgesic, alone or as part of multimodal analgesia. It has almost 10% analgesic activity of morphine. Similarly it has less adverse effects than other strong opioids such as fentanyl and morphine and can be safely used in patients with risk of respiratory depression. However two cases of respiratory depression had been reported. A 5.5 year boy in France was reported to develop respiratory depression after receiving 1 mg per kg of tramadol single dose orally (20 mg total). And he was found out to be ultra-rapid CYP2D6 genotype. This genotype results in rapid metabolism of tramadol to M1 which has high affinity for  $\mu$  receptors than the parent drug.<sup>9</sup>

Another patient was reported to develop respiratory depression after receiving tramadol by patient controlled analgesia. This patient was also found to be rapid metaboliser and his renal impairment resulted in accumulation of M1.<sup>10</sup> Both these patients were given naloxone and opioid overdose effects were completely reversed. Although in contrast to our study in these cases tramadol was given by oral or intravenous route, but these also show that tramadol can be associated with respiratory depression.

After the French child case, FDA also changed its comments about tramadol from "less respiratory depressant" to "it should be used cautiously in patients at risk of respiratory depression",<sup>11</sup> A retrospective study was conducted in Iran in which 1365 cases of poisoning below 12 years of age were included. 20 children ingested tramadol and out of those 3(15%) developed apnea.<sup>12</sup> Respiratory depression in these cases was also associated with oral administration as compared to our case in which it was associated with intrathecal route.

Opioids have been used along with local anesthetics in neuraxial anesthesia and analgesia. Their use prolongs the analgesic effects. However these are associated with few common side effects such as pruritus, nausea and vomiting. In a study incidence of nausea, vomiting, and pruritus after less than 0.3 mg of intrathecal morphine, was 21.5%, 14.8%, and 59.5% respectively.<sup>3</sup> Morphine is also associated with respiratory depression after intrathecal and epidural use and it requires vigilant monitoring.<sup>1,2,4</sup>

Tramadol is also being used in neuraxial anesthesia and studies have shown that it prolongs the analgesic effects. Considering that it is weak opioid and has less adverse effects than other opioids in usual clinical practice, it is assumed that it will have fewer adverse effects when used intrathecal or in epidural.<sup>6,7</sup>

However, like morphine and fentanyl, tramadol is also associated with pruritus, nausea and vomiting.<sup>13</sup> But these effects are mild than morphine and fentanyl and it is suggested that tramadol is better than fentanyl in terms of these side effects.<sup>14</sup>

As compared to our study, none of these studies showed respiratory depression after intrathecal administration. In our patient respiratory depression occurred after intrathecal administration of 20 mg of tramadol and these opioid overdose effects were terminated completely by inj naloxone. A study on rats showed that respiratory depressant effects of tramadol are potentiated by midazolam.<sup>15</sup>

We too, used midazolam 2 mg IV and it may have potentiated the effects. However, we consider that main drug responsible was intrathecal tramadol because opioid overdose effects were completely reversed with naloxone.

## CONCLUSION

Although tramadol is a weak opioid and not associated with respiratory depression in routine clinical use, but based upon our experience in the

above case report, we recommend that whenever tramadol is used intrathecally, vigilant monitoring should be exercised for early detection of any event of respiratory depression.

**Conflict of interest:** None declared by the authors

**Author contribution:** WA: managed the case, literature review, manuscript preparation

MAS: managed the case, helped in preparation of manuscript

KMY: helped in managing the case and preparation of manuscript

## REFERENCES

1. Crowgey TR, Dominguez JE, Peterson-Layne C, Allen TK, Muir HA, Habib AS. A retrospective assessment of the incidence of respiratory depression after neuraxial morphine administration for postcesarean delivery analgesia. *Anesth Analg* 2013 Dec;117(6):1368-70. doi: 10.1213/ANE.0b013e3182a9b042. [PubMed]
2. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression: finding the right balance. *Drugs* 2011 Oct 1;71(14):1807-19. doi: 10.2165/11596250-000000000-00000. [PubMed]
3. Chinachoti T, Nilrat P, Samarnpiboonphol P. Nausea, vomiting and pruritus induced by intrathecal morphine. *J Med Assoc Thai* 2013 May;96(5):589-94. [PubMed]
4. Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth* 2005 Nov;17(7):537-42. [PubMed]
5. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923. [PubMed]
6. Parthasarathy S, Ravishankar, M. Single dose intrathecal tramadol in the management of post appendectomy pain. *J Anaesthesiol Clin Pharmacol* 2002;18:419-422.
7. Chakraborty S, Chakrabarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. *Indian J Pharmacol.* 2008;40(4):180-182. doi: 10.4103/0253-7613.43166. [PubMed] [Free full text]
8. Teppema LJ, Nieuwenhuijs D, Olievier CN, Dahan A. Respiratory Depression by Tramadol in the Cat: Involvement of Opioid Receptors. *Anesthesiology* 2003;98(2):420-427. [PubMed] [Free full text]
9. Orliaguet G, Hamza J, Couloigner V, Denoyelle F, Lorient MA, Broly F, Garabedian EN. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics* 2015;135(3):e753-5. doi: 10.1542/peds.2014-2673. [PubMed] [Free full text]
10. Stamer UM, Stüber F, Muders T, Musshoff F. Respiratory depression with tramadol in a patient with renal impairment and CYP2D6 gene duplication. *Anesth Analg* 2008 Sep;107(3):926-9. doi: 10.1213/ane.0b013e31817b796e. [PubMed]
11. U.S. Comments to the Tramadol Critical Review Document. [Online]. [Cited 2017 Mar 30] Available from: [www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-sup0003-02.pdf](http://www.fda.gov/ohrms/dockets/dockets/05n0479/05N-0479-sup0003-02.pdf)
12. Hassanian-Moghaddam H, Farnaghi F, Rahimi M. Tramadol overdose and apnea in hospitalized children, a review of 20 cases. *Res Pharm Sci* 2015;10(6):544-552. [PubMed] [Free full text]
13. Chatrath V, Khetarpal R, Sharma S, Kumari P, Sudha, Bali K. Fentanyl versus tramadol with levobupivacaine for combined spinal-epidural analgesia in labor. *Saudi J Anaesth* 2015 Jul-Sep;9(3):263-267. doi: 10.4103/1658-354X.154700. [PubMed] [Free full text]
14. Afolayan JM, Olajumoke TO, Amadasun FE, Edomwonyi NP. Intrathecal tramadol versus intrathecal fentanyl for visceral pain control during bupivacaine subarachnoid block for open appendectomy. *Niger J Clin Pract* 2014 May-Jun;17(3):324-30. doi: 10.4103/1119-3077.130234. [PubMed] [Free full text]
15. Lagard C, Chevillard L, Malissin I, Risède P, Callebert J, Labat L, et al. Mechanisms of tramadol-related neurotoxicity in the rat: Does diazepam/tramadol combination play a worsening role in overdose? *Toxicol Appl Pharmacol* 2016 Nov;310:108-119. doi: 10.1016/j.taap.2016.09.013. [PubMed]

